The Applicants also discussed the 102 rejections, particularly based upon the teachings of injecting HGF in Akimoto. The Examiners appeared to be convinced that the amended claims are not anticipated by Akimoto since the patient population treated in the claims (suffering embolism) is different from the reference (normal subject).

The following remarks and attached publications are submitted in response to the Examiners' questions.

Re: Scientific publications which show that these tests are accepted in the art

(1) Exelon® (rivastigmine tartrate) by Novartis is indicated for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease. Please see page 13 of "Novartis T2006-73, Exelon® (rivastigmine tartrate) Capsules and Oral Solution; Prescribing information" (total 28 pages printed out from website, http://www.pharma.us.novartis.com/product/pi/pdf/exelon.pdf) enclosed herewith.

(2) As pre-clinical data of rivastigmine, the Morris water maze test has been mentioned in "Regulatory Rapporteur, CNS submissions 10 Years of EMEA CNS medicines-3 Anti-dementia treatments" (total 6 pages printed out from website, http://www.eolasbio.co.uk/pdf/3_EMEA_Alz_2006.pdf) enclosed herewith.

See the front page, middle column, lines 10-15 of this publication, which mentions that "Rivastigmine reversed the impairments of memory function induced by administration of the muscarinic cholinergic antagonist scopolamine in rats tested in the Morris water maze test (Ballard and McAllister, 1999)."

Further, the "Clinical Efficacy of Rivastigmine" is described on page 2, middle to right columns of this publication.

The Applicants respectfully submit that these publications show that the Morris water maze test is accepted in the art as a model for treatment of human conditions.

Re: How the rat tests showed effectiveness of improving mental conditions

One of the present inventors, Dr. Satoshi Takeo believes that the result of Morris water maze test shown in the Rule 1.132 Declaration submitted with Applicants' last response can be used as a pre-clinical data for a clinical data of human dementia.

Applicants propose to contact the Examiner to discuss whether a further Rule 1.132 Declaration stating how the rat tests showed effectiveness of improving mental condition might be helpful.

Respectfully submitted,

Satoshi TAKEO et al.

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August 8, 2008

NOVARTIS

T2006-73

Exelon®

(rivastigmine tartrate)

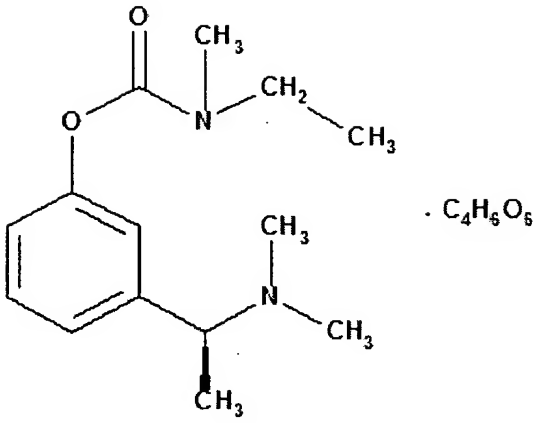
Capsules and Oral Solution

Rx only

Prescribing Information

DESCRIPTION

Exelon® (rivastigmine tartrate) is a reversible cholinesterase inhibitor and is known chemically as (S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate hydrogen-(2R,3R)-tartrate. Rivastigmine tartrate is commonly referred to in the pharmacological literature as SDZ ENA 713 or ENA 713. It has an empirical formula of $C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$ (hydrogen tartrate salt – hta salt) and a molecular weight of 400.43 (hta salt). Rivastigmine tartrate is a white to off-white, fine crystalline powder that is very soluble in water, soluble in ethanol and acetonitrile, slightly soluble in n-octanol and very slightly soluble in ethyl acetate. The distribution coefficient at 37°C in n-octanol/phosphate buffer solution pH 7 is 3.0.



Exelon Capsules contain rivastigmine tartrate, equivalent to 1.5, 3, 4.5 and 6 mg of rivastigmine base for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. Each hard-gelatin capsule contains gelatin, titanium dioxide and red and/or yellow iron oxides.

Exelon Oral Solution is supplied as a solution containing rivastigmine tartrate, equivalent to 2 mg/mL of rivastigmine base for oral administration. Inactive ingredients are citric acid, D&C yellow #10, purified water, sodium benzoate and sodium citrate.

CLINICAL PHARMACOLOGY

Mechanism of Action

Pathological changes in dementia of the Alzheimer's type and dementia associated with Parkinson's disease involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are thought to be intricately involved in memory, attention, learning, and other cognitive processes. While the precise mechanism of rivastigmine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this proposed mechanism is correct, Exelon's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process. After a 6-mg dose of rivastigmine, anticholinesterase activity is present in CSF for about 10 hours, with a maximum inhibition of about 60% 5 hours after dosing.

In vitro and *in vivo* studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concomitant administration of memantine, an N-methyl-D-aspartate receptor antagonist.

Clinical Trial Data

Dementia of the Alzheimer's Type

The effectiveness of Exelon® (rivastigmine tartrate) as a treatment for Alzheimer's disease is demonstrated by the results of 2 randomized, double-blind, placebo-controlled clinical investigations in patients with Alzheimer's disease [diagnosed by NINCDS-ADRDA and DSM-IV criteria, Mini-Mental State Examination (MMSE) =10 and =26, and the Global Deterioration Scale (GDS)]. The mean age of patients participating in Exelon trials was 73 years with a range of 41-95. Approximately 59% of patients were women and 41% were men. The racial distribution was Caucasian 87%, Black 4% and other races 9%.

Study Outcome Measures

In each study, the effectiveness of Exelon was evaluated using a dual outcome assessment strategy.

The ability of Exelon to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on ADAS-cog of approximately 23 units, with a range from 1 to 61. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's disease suggests that they gain 6-12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in Exelon trials was approximately 3-8 units per year.

The ability of Exelon to produce an overall clinical effect was assessed using a Clinician's Interview-Based Impression of Change (CIBIC) that required the use of caregiver information, the CIBIC-Plus. The CIBIC-Plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-Plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC-Plus evaluations from other clinical trials. The CIBIC-Plus used in the Exelon trials was a structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of three domains: patient cognition, behavior and functioning, including assessment of activities of daily living. It represents the assessment of a skilled clinician using validated scales based on his/her observation at interviews conducted separately

with the patient and the caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-Plus is scored as a 7-point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening." The CIBIC-Plus has not been systematically compared directly to assessments not using information from caregivers or other global methods.

U.S. 26-Week Study

In a study of 26 weeks duration, 699 patients were randomized to either a dose range of 1-4 mg or 6-12 mg of Exelon per day or to placebo, each given in divided doses. The 26-week study was divided into a 12-week forced-dose titration phase and a 14-week maintenance phase. The patients in the active treatment arms of the study were maintained at their highest tolerated dose within the respective range.

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the Exelon-treated patients compared to the patients on placebo were 1.9 and 4.9 units for the 1-4 mg and 6-12 mg treatments, respectively. Both treatments were statistically significantly superior to placebo and the 6-12 mg/day range was significantly superior to the 1-4 mg/day range.

Figure 1: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

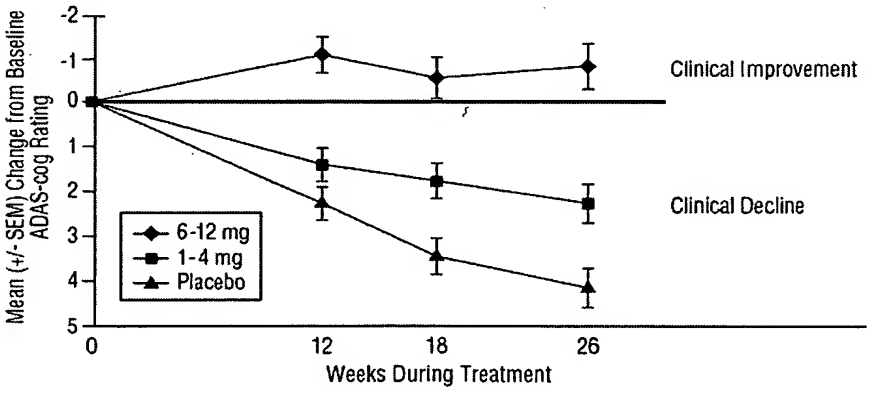
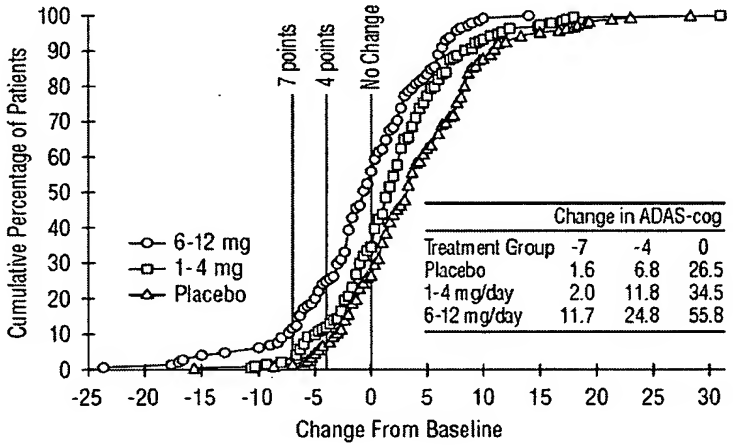


Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

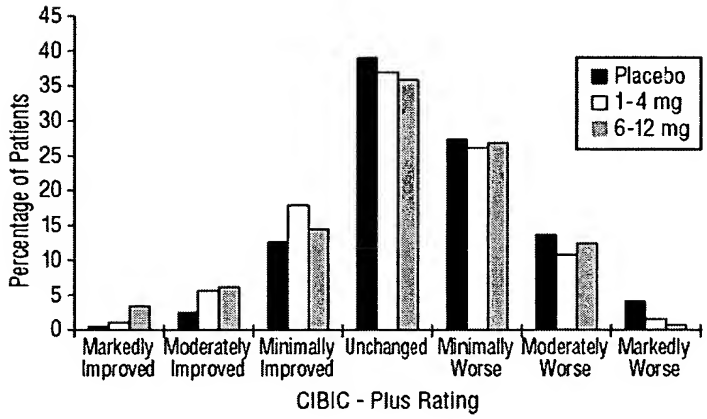
The curves demonstrate that both patients assigned to Exelon and placebo have a wide range of responses, but that the Exelon groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

Figure 2: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 84%, 1-4 mg 85%, and 6-12 mg 65%.



Effects on the CIBIC-Plus: Figure 3 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean Exelon-placebo differences for these groups of patients in the mean rating of change from baseline were 0.32 units and 0.35 units for 1-4 mg and 6-12 mg of Exelon, respectively. The mean ratings for the 6-12 mg/day and 1-4 mg/day groups were statistically significantly superior to placebo. The differences between the 6-12 mg/day and the 1-4 mg/day groups were statistically significant.

Figure 3: Frequency Distribution of CIBIC-Plus Scores at Week 26



Global 26-Week Study

In a second study of 26 weeks duration, 725 patients were randomized to either a dose range of 1-4 mg or 6-12 mg of Exelon per day or to placebo, each given in divided doses. The 26-week study was divided into a 12-week forced-dose titration phase and a 14-week maintenance phase. The patients in the active treatment arms of the study were maintained at their highest tolerated dose within the respective range.

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the Exelon-treated patients compared to the patients on placebo were 0.2 and 2.6 units for the 1-4 mg and 6-12 mg treatments, respectively. The 6-12 mg/day group was statistically significantly superior to placebo, as well as to the 1-4 mg/day group. The difference between the 1-4 mg/day group and placebo was not statistically significant.

Figure 4: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

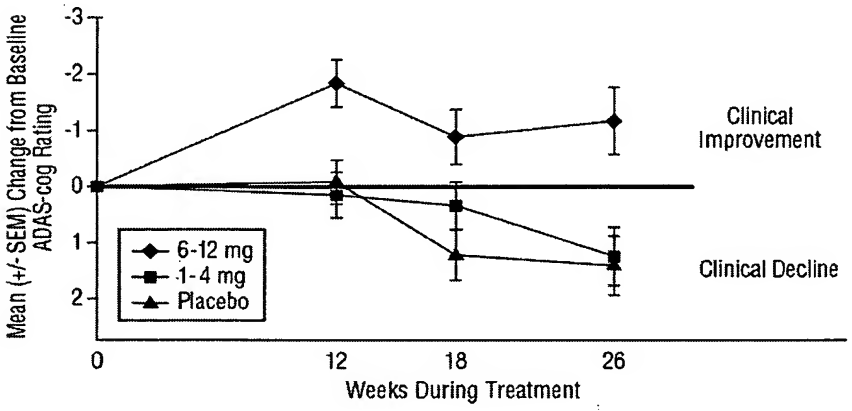
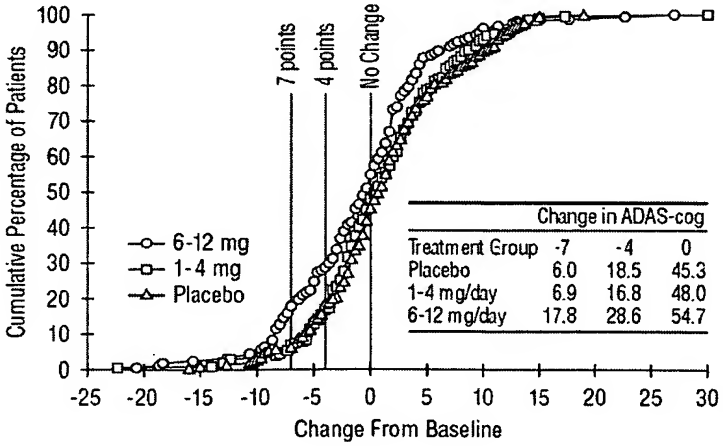


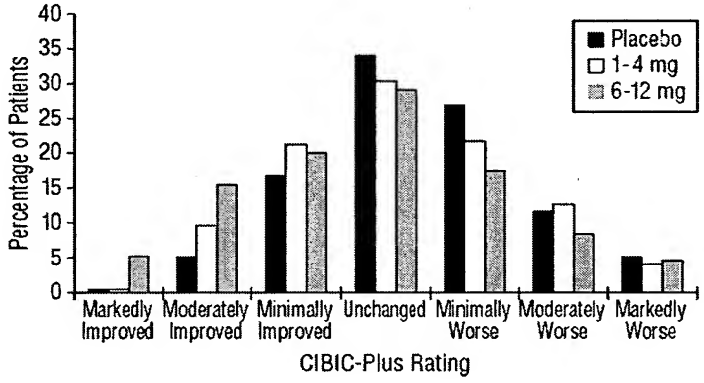
Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Similar to the U.S. 26-week study, the curves demonstrate that both patients assigned to Exelon and placebo have a wide range of responses, but that the 6-12 mg/day Exelon group is more likely to show the greater improvements.

Figure 5: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 87%, 1-4 mg 86%, and 6-12 mg 67%.



Effects on the CIBIC-Plus: Figure 6 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean Exelon-placebo differences for these groups of patients for the mean rating of change from baseline were 0.14 units and 0.41 units for 1-4 mg and 6-12 mg of Exelon, respectively. The mean ratings for the 6-12 mg/day group were statistically significantly superior to placebo. The comparison of the mean ratings for the 1-4 mg/day group and placebo group was not statistically significant.

Figure 6: Frequency Distribution of CIBIC-Plus Scores at Week 26



U.S. Fixed-Dose Study

In a study of 26 weeks duration, 702 patients were randomized to doses of 3, 6, or 9 mg/day of Exelon or to placebo, each given in divided doses. The fixed-dose study design, which included a 12-week forced-dose titration phase and a 14-week maintenance phase, led to a high dropout rate in the 9 mg/day group because of poor tolerability. At 26 weeks of treatment, significant differences were observed for the ADAS-cog mean change from baseline for the 9 mg/day and 6 mg/day groups, compared to placebo. No significant differences were observed between any of the Exelon-dose groups and placebo for the analysis of the CIBIC-Plus mean rating of change. Although no significant differences were observed between Exelon treatment groups, there was a trend toward numerical superiority with higher doses.

Dementia Associated with Parkinson's Disease (PDD)

International 24-Week Study

The effectiveness of Exelon as a treatment for dementia associated with Parkinson's disease is demonstrated by the results of one randomized, double-blind, placebo-controlled clinical investigation in patients with mild to moderate dementia, with onset at least 2 years after the initial diagnosis of idiopathic Parkinson's disease. The diagnosis of idiopathic Parkinson's disease was based on the United Kingdom Parkinson's Disease Society Brain Bank clinical criteria. The diagnosis of dementia was based on the criteria stipulated under the DSM-IV category "Dementia Due To Other General Medical Condition" (code 294.1x), but patients were not required to have a distinctive pattern of cognitive deficits as part of the dementia. Alternate causes of dementia were excluded by clinical history, physical and neurological examination, brain imaging, and relevant blood tests. Patients enrolled in the study had a MMSE score $\geq$10 and $\leq$24 at entry. The mean age of patients participating in this trial was 72.7 years with a range of 50–91. Approximately, 35.1% of patients were women and 64.9% of patients were men. The racial distribution was 99.6% Caucasian and other races 0.4%.

Study Outcome Measures

This study used a dual outcome assessment strategy to evaluate the effectiveness of Exelon.

The ability of Exelon to improve cognitive performance was assessed with the ADAS-cog.

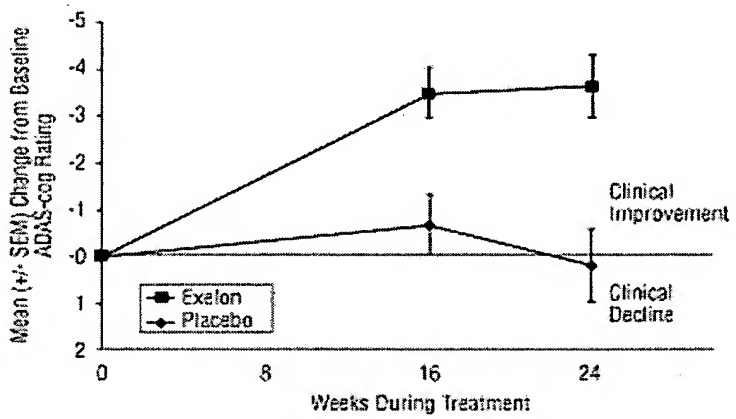
The ability of Exelon to produce an overall clinical effect was assessed using the Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change (ADCS-CGIC). The ADCS-CGIC is a more standardized form of CIBIC-Plus and is also scored as a 7-point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening."

Study Results

In this study, 541 patients were randomized to a dose range of 3–12 mg of Exelon per day or to placebo in a ratio of 2:1, given in divided doses. The 24-week study was divided into a 16-week titration phase and an 8-week maintenance phase. The patients in the active treatment arm of the study were maintained at their highest tolerated dose within the specified dose range.

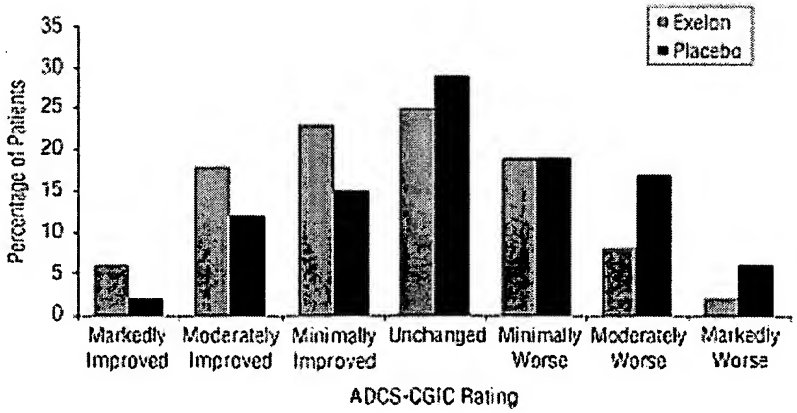
Effects on the ADAS-cog: Figure 7 illustrates the time course for the change from baseline in ADAS-cog scores for both treatment groups over the 24-week study. At 24 weeks of treatment, the mean difference in the ADAS-cog change scores for the Exelon-treated patients compared to the patients on placebo was 3.8 points. This treatment difference was statistically significant in favor of Exelon when compared to placebo.

Figure 7: Time Course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment



Effects on the ADCS-CGIC: Figure 8 is a histogram of the distribution of patients' scores on the ADCS-CGIC (Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change) at 24 weeks. The mean difference in change scores between the Exelon and placebo groups from baseline was 0.5 points. This difference was statistically significant in favor of Exelon treatment.

Figure 8: Distribution of ADCS-CGIC Scores for Patients Completing 24 Weeks of Treatment



Age, Gender and Race

Patients' age, gender, or race did not predict clinical outcome of Exelon treatment.

Pharmacokinetics

Rivastigmine is well absorbed with absolute bioavailability of about 40% (3-mg dose). It shows linear pharmacokinetics up to 3 mg BID but is non-linear at higher doses. Doubling the dose from 3 to 6 mg BID results in a 3-fold increase in AUC. The elimination half-life is about 1.5 hours, with most elimination as metabolites via the urine.

Absorption: Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. Absolute bioavailability after a 3-mg dose is about 36%. Administration of Exelon with food delays absorption (t_{max}) by 90 minutes, lowers C_{max} by approximately 30% and increases AUC by approximately 30%.

Distribution: Rivastigmine is widely distributed throughout the body with a volume of distribution in the range of 1.8-2.7 L/kg. Rivastigmine penetrates the blood brain barrier, reaching CSF peak concentrations in 1.4-2.6 hours. Mean $AUC_{1\text{-}12hr}$ ratio of CSF/plasma averaged 40 ± 0.5% following 1-6 mg BID doses.

Rivastigmine is about 40% bound to plasma proteins at concentrations of 1-400 ng/mL, which cover the therapeutic concentration range. Rivastigmine distributes equally between blood and plasma with a blood-to-plasma partition ratio of 0.9 at concentrations ranging from 1-400 ng/mL.

Metabolism: Rivastigmine is rapidly and extensively metabolized, primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. Based on evidence from in vitro and animal studies, the major cytochrome P450 isozymes are minimally involved in rivastigmine metabolism. Consistent with these observations is the finding that no drug interactions related to cytochrome P450 have been observed in humans (see Drug-Drug Interactions).

Elimination: The major pathway of elimination is via the kidneys. Following administration of ^{14}C-rivastigmine to 6 healthy volunteers, total recovery of radioactivity over 120 hours was 97% in urine and 0.4% in feces. No parent drug was detected in urine. The sulfate conjugate of the decarbamylated metabolite is the major component excreted in urine and represents 40% of the dose. Mean oral clearance of rivastigmine is 1.8 ± 0.6 L/min after 6 mg BID.

Special Populations

Hepatic Disease: Following a single 3-mg dose, mean oral clearance of rivastigmine was 60% lower in hepatically impaired patients (n=10, biopsy proven) than in healthy subjects (n=10). After multiple 6-mg BID oral dosing, the mean clearance of rivastigmine was 65% lower in mild (n=7, Child-Pugh score 5-6) and moderate (n=3, Child-Pugh score 7-9) hepatically impaired patients (biopsy proven, liver cirrhosis) than in healthy subjects (n=10). Dosage

adjustment is not necessary in hepatically impaired patients as the dose of drug is individually titrated to tolerability.

Renal Disease: Following a single 3-mg dose, mean oral clearance of rivastigmine is 64% lower in moderately impaired renal patients (n=8, GFR=10-50 mL/min) than in healthy subjects (n=10, GFR =60 mL/min); Cl/F=1.7 L/min (cv=45%) and 4.8 L/min (cv=80%), respectively. In severely impaired renal patients (n=8, GFR <10 mL/min), mean oral clearance of rivastigmine is 43% higher than in healthy subjects (n=10, GFR =60 mL/min); Cl/F=6.9 L/min and 4.8 L/min, respectively. For unexplained reasons, the severely impaired renal patients had a higher clearance of rivastigmine than moderately impaired patients. However, dosage adjustment may not be necessary in renally impaired patients as the dose of the drug is individually titrated to tolerability.

Age: Following a single 2.5-mg oral dose to elderly volunteers (>60 years of age, n=24) and younger volunteers (n=24), mean oral clearance of rivastigmine was 30% lower in elderly (7 L/min) than in younger subjects (10 L/min).

Gender and Race: No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of Exelon, but a population pharmacokinetic analysis indicates that gender (n=277 males and 348 females) and race (n=575 White, 34 Black, 4 Asian, and 12 Other) did not affect the clearance of Exelon.

Nicotine Use: Population PK analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% (n=75 Smokers and 549 Nonsmokers).

Drug-Drug Interactions

Effect of Exelon on the Metabolism of Other Drugs: Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on in vitro studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP 1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Exelon.

Effect of Other Drugs on the Metabolism of Exelon: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single-dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), ß-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal

antiinflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15). In addition, in clinical trials, no increased risk of clinically relevant untoward effects was observed in patients treated concomitantly with Exelon and these agents.

INDICATIONS AND USAGE

Exelon® (rivastigmine tartrate) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

Exelon® (rivastigmine tartrate) is indicated for the treatment of mild to moderate dementia associated with Parkinson's disease.

The dementia of Parkinson's disease is purportedly characterized by impairments in executive function, memory retrieval, and attention in patients with an established diagnosis of Parkinson's disease. The diagnosis of the dementia of Parkinson's disease, however, can reliably be made in patients in whom a progressive dementia syndrome occurs (without the necessity to document the specific deficits described above) at least 2 years after a diagnosis of Parkinson's disease has been made, and in whom other causes of dementia have been ruled out (see CLINICAL PHARMACOLOGY, Clinical Trial Data).

CONTRAINDICATIONS

Exelon® (rivastigmine tartrate) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation (see DESCRIPTION).

WARNINGS

Gastrointestinal Adverse Reactions

Exelon® (rivastigmine tartrate) use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. For this reason, patients should always be started at a dose of 1.5 mg BID and titrated to their maintenance dose. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose (see DOSAGE AND ADMINISTRATION) to reduce the possibility of severe vomiting and its potentially serious sequelae (e.g., there has been one postmarketing report of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment with a 4.5-mg dose after 8 weeks of treatment interruption).

Nausea and Vomiting: **In the controlled clinical trials, 47% of the patients treated with an Exelon dose in the therapeutic range of 6-12 mg/day (n=1189) developed nausea (compared with 12% in placebo). A total of 31% of Exelon-treated patients developed at least one episode of vomiting (compared with 6% for placebo). The rate of vomiting was higher during the titration phase (24% vs. 3% for placebo) than in the maintenance phase (14% vs. 3% for placebo). The rates were higher in women than men. Five percent of patients discontinued for vomiting, compared to less than 1% for patients on placebo. Vomiting was severe in 2% of Exelon-treated patients and was rated as mild or moderate each in 14% of patients. The rate of nausea was higher during the titration phase (43% vs. 9% for placebo) than in the maintenance phase (17% vs. 4% for placebo).**

Weight Loss: **In the controlled trials, approximately 26% of women on high doses of Exelon (greater than 9 mg/day) had weight loss equal to or greater than 7% of their baseline weight compared to 6% in the placebo-treated patients. About 18% of the males in the high-dose group experienced a similar degree of weight loss compared to 4% in placebo-treated patients. It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.**

Anorexia: In the controlled clinical trials, of the patients treated with an Exelon dose of 6-12 mg/day, 17% developed anorexia compared to 3% of the placebo patients. Neither the time course nor the severity of the anorexia is known.

Peptic Ulcers/Gastrointestinal Bleeding: Because of their pharmacological action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal antiinflammatory drugs (NSAIDs). Clinical studies of Exelon have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Anesthesia

Exelon as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions

Drugs that increase cholinergic activity may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials, Exelon was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities. Syncopal episodes have been reported in 3% of patients receiving 6-12 mg/day of Exelon, compared to 2% of placebo patients.

Genitourinary

Although this was not observed in clinical trials of Exelon, drugs that increase cholinergic activity may cause urinary obstruction.

Neurological Conditions

Seizures: Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer's disease.

Pulmonary Conditions

Like other drugs that increase cholinergic activity, Exelon should be used with care in patients with a history of asthma or obstructive pulmonary disease.

PRECAUTIONS

Information for Patients and Caregivers

Caregivers should be advised of the high incidence of nausea and vomiting associated with the use of the drug along with the possibility of anorexia and weight loss. Caregivers should be encouraged to monitor for these adverse events and inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than several days, the next dose should not be administered until they have discussed this with the physician.

Caregivers should be instructed in the correct procedure for administering Exelon® (rivastigmine tartrate) Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering Exelon Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

Caregivers and patients should be advised that like other cholinomimetics, Exelon® may exacerbate or induce extrapyramidal symptoms. Worsening in patients with Parkinson's disease, including an increased incidence or intensity of tremor, has been observed.

Drug-Drug Interactions

Effect of Exelon on the Metabolism of Other Drugs: Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on in vitro studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The

elevation of prothrombin time induced by warfarin is not affected by administration of Exelon.

Effect of Other Drugs on the Metabolism of Exelon: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single-dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), ß-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal antiinflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15).

Use with Anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In carcinogenicity studies conducted at dose levels up to 1.1 mg-base/kg/day in rats and 1.6 mg-base/kg/day in mice, rivastigmine was not carcinogenic. These dose levels are approximately 0.9 times and 0.7 times the maximum recommended human daily dose of 12 mg/day on a mg/m^2 basis.

Rivastigmine was clastogenic in two in vitro assays in the presence, but not the absence, of metabolic activation. It caused structural chromosomal aberrations in V79 Chinese hamster lung cells and both structural and numerical (polyploidy) chromosomal aberrations in human peripheral blood lymphocytes. Rivastigmine was not genotoxic in three in vitro assays: the Ames test, the unscheduled DNA synthesis (UDS) test in rat hepatocytes (a test for induction of DNA repair synthesis), and the HGPRT test in V79 Chinese hamster cells. Rivastigmine was not clastogenic in the in vivo mouse micronucleus test.

Rivastigmine had no effect on fertility or reproductive performance in the rat at dose levels up to 1.1 mg-base/kg/day. This dose is approximately 0.9 times the maximum recommended human daily dose of 12 mg/day on a mg/m^2 basis.

Pregnancy

Pregnancy Category B: Reproduction studies conducted in pregnant rats at doses up to 2.3 mg-base/kg/day (approximately 2 times the maximum recommended human dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 2.3 mg-base/kg/day (approximately 4 times the maximum recommended human dose on a mg/m^2 basis) revealed no evidence of teratogenicity. Studies in

rats showed slightly decreased fetal/pup weights, usually at doses causing some maternal toxicity; decreased weights were seen at doses which were several fold lower than the maximum recommended human dose on a mg/m^2 basis. There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Exelon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether rivastigmine is excreted in human breast milk. Exelon has no indication for use in nursing mothers.

Pediatric Use

There are no adequate and well-controlled trials documenting the safety and efficacy of Exelon in any illness occurring in children.

ADVERSE REACTIONS

Dementia of the Alzheimer's Type

Adverse Events Leading to Discontinuation

The rate of discontinuation due to adverse events in controlled clinical trials of Exelon® (rivastigmine tartrate) was 15% for patients receiving 6-12 mg/day compared to 5% for patients on placebo during forced weekly dose titration. While on a maintenance dose, the rates were 6% for patients on Exelon compared to 4% for those on placebo.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Clinical Trials during Titration and Maintenance in Patients Receiving 6-12 mg/day Exelon® Using a Forced-Dose Titration

Study Phase	Titration		Maintenance		Overall	
	Placebo (n=868)	Exelon® =6-12 mg/day (n=1,189)	Placebo (n=788)	Exelon® =6-12 mg/day (n=987)	Placebo (n=868)	Exelon® =6-12 mg/day (n=1,189)
Event/% Discontinuing						
Nausea	<1	8	<1	1	1	8
Vomiting	<1	4	<1	1	<1	5
Anorexia	0	2	<1	1	<1	3
Dizziness	<1	2	<1	1	<1	2

Most Frequent Adverse Clinical Events Seen in Association with the Use of Exelon

The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by Exelon's cholinergic effects. These include nausea, vomiting, anorexia, dyspepsia, and asthenia.

Gastrointestinal Adverse Reactions: Exelon use is associated with significant nausea, vomiting, and weight loss (see WARNINGS).

Adverse Events Reported in Controlled Trials

Table 2 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with Exelon doses of 6-12 mg/day than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

In general, adverse reactions were less frequent later in the course of treatment.

No systematic effect of race or age could be determined from the incidence of adverse events in the controlled studies. Nausea, vomiting and weight loss were more frequent in women than men.

Table 2. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Exelon® (6-12 mg/day) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=868)	Exelon® (6-12 mg/day) (n=1,189)
Percent of Patients with any Adverse Event	79	92
Autonomic Nervous System		
Sweating Increased	1	4
Syncope	2	3
Body as a Whole		
Accidental Trauma	9	10
Fatigue	5	9

Asthenia	2	6
Malaise	2	5
Influenza-like Symptoms	2	3
Weight Decrease	<1	3
Cardiovascular Disorders, General		
Hypertension	2	3
Central and Peripheral Nervous System		
Dizziness	11	21
Headache	12	17
Somnolence	3	5
Tremor	1	4
Gastrointestinal System		
Nausea	12	47
Vomiting	6	31
Diarrhea	11	19
Anorexia	3	17
Abdominal Pain	6	13
Dyspepsia	4	9
Constipation	4	5
Flatulence	2	4
Eructation	1	2
Psychiatric Disorders		
Insomnia	7	9
Confusion	7	8
Depression	4	6
Anxiety	3	5
Hallucination	3	4
Aggressive Reaction	2	3
Resistance Mechanism Disorders		
Urinary Tract Infection	6	7
Respiratory System		
Rhinitis	3	4

Other adverse events observed at a rate of 2% or more on Exelon 6-12 mg/day but at a greater or equal rate on placebo were chest pain, peripheral edema, vertigo, back pain, arthralgia, pain, bone fracture, agitation, nervousness, delusion, paranoid reaction, upper respiratory tract infection, infection (general), coughing, pharyngitis, bronchitis, rash (general), urinary incontinence.

Dementia Associated with Parkinson's Disease

Adverse Events Leading to Discontinuation

The rate of discontinuation due to adverse events in the single controlled trial of Exelon (rivastigmine tartrate) was 18.2% for patients receiving 3-12 mg/day compared to 11.2% for patients on placebo during the 24-week study.

The most frequent adverse events that led to discontinuation from this study, defined as those occurring in at least 1% of patients receiving Exelon and more frequent than those receiving placebo, were nausea (3.6% Exelon vs. 0.6% placebo), vomiting (1.9% Exelon vs. 0.6% placebo), and tremor (1.7% Exelon vs. 0.0% placebo).

Most Frequent Adverse Clinical Events Seen in Association with the Use of Exelon

The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by Exelon's cholinergic effects. These include nausea, vomiting, tremor, anorexia, and dizziness.

Adverse Events Reported in Controlled Trials

Table 3 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with Exelon doses of 3-12 mg/day than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

In general, adverse reactions were less frequent later in the course of treatment.

Table 3. Adverse Events Reported in the Single Controlled Clinical Trial in at Least 2% of Patients Receiving Exelon® (3-12 mg/day) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=179)	Exelon® (3-12 mg/day) (n=362)
Percent of Patients with any Adverse Event	71	84
Gastrointestinal Disorders		
Nausea	11	29
Vomiting	2	17
Diarrhea	4	7
Upper Abdominal Pain	1	4
General Disorders and Administrative Site Conditions		
Fatigue	3	4
Asthenia	1	2
Metabolism and Nutritional Disorders		
Anorexia	3	6
Dehydration	1	2
Nervous System Disorders		
Tremor	4	10
Dizziness	1	6
Headache	3	4
Somnolence	3	4
Parkinson's Disease (worsening)	1	3
Parkinsonism	1	2

Psychiatric Disorders		
Anxiety	1	4
Insomnia	2	3

Other Adverse Events Observed During Clinical Trials

Dementia of the Alzheimer's Type

Exelon has been administered to over 5,297 individuals during clinical trials worldwide. Of these, 4,326 patients have been treated for at least 3 months, 3,407 patients have been treated for at least 6 months, 2,150 patients have been treated for 1 year, 1,250 patients have been treated for 2 years, and 168 patients have been treated for over 3 years. With regard to exposure to the highest dose, 2,809 patients were exposed to doses of 10-12 mg, 2,615 patients treated for 3 months, 2,328 patients treated for 6 months, 1,378 patients treated for 1 year, 917 patients treated for 2 years, and 129 patients treated for over 3 years.

Treatment-emergent signs and symptoms that occurred during 8 controlled clinical trials and 9 open-label trials in North America, Western Europe, Australia, South Africa, and Japan were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified WHO dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 5,297 patients from these trials who experienced that event while receiving Exelon. All adverse events occurring in at least 6 patients (approximately 0.1%) are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, relatively minor events, or events unlikely to be drug-caused. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1,000 patients. These adverse events are not necessarily related to Exelon treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: *Infrequent:* Cold clammy skin, dry mouth, flushing, increased saliva.

Body as a Whole: *Frequent:* Accidental trauma, fever, edema, allergy, hot flushes, rigors. *Infrequent:* Edema periorbital or facial, hypothermia, edema, feeling cold, halitosis.

Cardiovascular System: *Frequent:* Hypotension, postural hypotension, cardiac failure.

Central and Peripheral Nervous System: *Frequent:* Abnormal gait, ataxia, paresthesia, convulsions. *Infrequent:* Paresis, apraxia, aphasia, dysphonia,

hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, migraine, neuralgia, nystagmus, peripheral neuropathy.

Endocrine System: *Infrequent:* Goiter, hypothyroidism.

Gastrointestinal System: *Frequent:* Fecal incontinence, gastritis. *Infrequent:* Dysphagia, esophagitis, gastric ulcer, gastroesophageal reflux, GI hemorrhage, hernia, intestinal obstruction, melena, rectal hemorrhage, gastroenteritis, ulcerative stomatitis, duodenal ulcer, hematemesis, gingivitis, tenesmus, pancreatitis, colitis, glossitis.

Hearing and Vestibular Disorders: *Frequent:* Tinnitus.

Heart Rate and Rhythm Disorders: *Frequent:* Atrial fibrillation, bradycardia, palpitation. *Infrequent:* AV block, bundle branch block, sick sinus syndrome, cardiac arrest, supraventricular tachycardia, extrasystoles, tachycardia.

Liver and Biliary System Disorders: *Infrequent:* Abnormal hepatic function, cholecystitis.

Metabolic and Nutritional Disorders: *Frequent:* Dehydration, hypokalemia. *Infrequent:* Diabetes mellitus, gout, hypercholesterolemia, hyperlipemia, hypoglycemia, cachexia, thirst, hyperglycemia, hyponatremia.

Musculoskeletal Disorders: *Frequent:* Arthritis, leg cramps, myalgia. *Infrequent:* Cramps, hernia, muscle weakness.

Myo-, Endo-, Pericardial and Valve Disorders: *Frequent:* Angina pectoris, myocardial infarction.

Platelet, Bleeding, and Clotting Disorders: *Frequent:* Epistaxis. *Infrequent:* Hematoma, thrombocytopenia, purpura.

Psychiatric Disorders: *Frequent:* Paranoid reaction, confusion. *Infrequent:* Abnormal dreaming, amnesia, apathy, delirium, dementia, depersonalization, emotional lability, impaired concentration, decreased libido, personality disorder, suicide attempt, increased libido, neurosis, suicidal ideation, psychosis.

Red Blood Cell Disorders: *Frequent:* Anemia. *Infrequent:* Hypochromic anemia.

Reproductive Disorders (Female & Male): *Infrequent:* Breast pain, impotence, atrophic vaginitis.

Resistance Mechanism Disorders: *Infrequent:* Cellulitis, cystitis, herpes simplex, otitis media.

Respiratory System: *Infrequent:* Bronchospasm, laryngitis, apnea.

Skin and Appendages: *Frequent:* Rashes of various kinds (maculopapular, eczema, bullous, exfoliative, psoriaform, erythematous). *Infrequent:* Alopecia, skin ulceration, urticaria, contact dermatitis.

Special Senses: *Infrequent:* Perversion of taste, loss of taste.

Urinary System Disorders: *Frequent:* Hematuria. *Infrequent:* Albuminuria, oliguria, acute renal failure, dysuria, micturition urgency, nocturia, polyuria, renal calculus, urinary retention.

Vascular (extracardiac) Disorders: *Infrequent:* Hemorrhoids, peripheral ischemia, pulmonary embolism, thrombosis, deep thrombophlebitis, aneurysm, intracranial hemorrhage.

Vision Disorders: *Frequent:* Cataract. *Infrequent:* Conjunctival hemorrhage, blepharitis, diplopia, eye pain, glaucoma.

White Cell and Resistance Disorders: *Infrequent:* Lymphadenopathy, leukocytosis.

Dementia Associated with Parkinson's Disease

Exelon has been administered to 485 individuals during clinical trials worldwide. Of these, 413 patients have been treated for at least 3 months, 253 patients have been treated for at least 6 months, and 113 patients have been treated for 1 year.

Additional treatment-emergent adverse events in patients with Parkinson's disease dementia occurring in at least 1 patient (approximately 0.3%) are listed below, excluding events that are already listed above for the dementia of the Alzheimer's type or elsewhere in labeling, WHO terms too general to be informative, relatively minor events, or events unlikely to be drug-caused. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1,000 patients. These adverse events are not necessarily related to Exelon treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Cardiovascular System: *Frequent:* Chest pain. *Infrequent:* Sudden cardiac death.

Central and Peripheral Nervous System: *Frequent:* Dyskinesia, bradykinesia, restlessness, transient ischemic attack. *Infrequent:* Dystonia, hemiparesis, epilepsy, restless leg syndrome.

Endocrine System: *Infrequent:* Elevated prolactin level.

Gastrointestinal System: *Frequent:* Dyspepsia. *Infrequent:* Fecaloma, dysphagia, diverticulitis, peritonitis.

Hearing and Vestibular Disorders: *Frequent:* Vertigo. *Infrequent:* Meniere's disease.

Heart Rate and Rhythm Disorders: *Infrequent:* Adam-Stokes syndrome.

Liver and Biliary System Disorders: *Infrequent:* Elevated alkaline phosphatase level, elevated gamma-glutamyltransferase level.

Musculoskeletal Disorders: *Frequent:* Back pain. *Infrequent:* Muscle stiffness, myoclonus, freezing phenomenon.

Psychiatric Disorders: *Frequent:* Agitation, depression. *Infrequent:* Delusion, insomnia.

Reproductive Disorders (Female & Male): *Infrequent:* endometrial hypertrophy, mastitis, prostatic adenoma.

Respiratory System: *Frequent:* Dyspnea. *Infrequent:* Cough.

Urinary System Disorders: *Infrequent:* Urinary incontinence, neurogenic bladder.

Vascular (extracardiac) Disorders: *Infrequent:* Vasovagal syncope, vasculitis.

Vision Disorders: *Infrequent:* Blurred vision, blepharospasm, conjunctivitis, retinopathy.

Post-Introduction Reports

Voluntary reports of adverse events temporally associated with Exelon that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following:

Skin and Appendages: Stevens-Johnson syndrome.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.

As Exelon® (rivastigmine tartrate) has a short plasma half-life of about one hour and a moderate duration of acetylcholinesterase inhibition of 8-10 hours, it is recommended that in cases of asymptomatic overdoses, no further dose of Exelon should be administered for the next 24 hours.

As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Atypical responses in blood pressure and heart rate have been reported with other drugs that increase cholinergic activity when coadministered with quaternary anticholinergics such as glycopyrrolate. Due to the short half-life of Exelon, dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose.

In overdoses accompanied by severe nausea and vomiting, the use of antiemetics should be considered. In a documented case of a 46-mg overdose with Exelon, the patient experienced vomiting, incontinence, hypertension,

psychomotor retardation, and loss of consciousness. The patient fully recovered within 24 hours and conservative management was all that was required for treatment.

DOSAGE AND ADMINISTRATION

Dementia of the Alzheimer's Type

The dosage of Exelon® (rivastigmine tartrate) shown to be effective in controlled clinical trials in Alzheimer's disease is 6-12 mg/day, given as twice-a-day dosing (daily doses of 3 to 6 mg BID). There is evidence from the clinical trials that doses at the higher end of this range may be more beneficial.

The starting dose of Exelon is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of 2 weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID and 6 mg BID should be attempted after a minimum of 2 weeks at the previous dose. If adverse effects (e.g., nausea, vomiting, abdominal pain, loss of appetite) cause intolerance during treatment, the patient should be instructed to discontinue treatment for several doses and then restart at the same or next lower dose level. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose and titrated as described above (see WARNINGS). The maximum dose is 6 mg BID (12 mg/day).

Dementia Associated with Parkinson's Disease

The dosage of Exelon shown to be effective in the single controlled clinical trial conducted in dementia associated with Parkinson's disease is 3-12 mg/day, given as twice-a-day dosing (daily doses of 1.5-6 mg BID). In that medical condition, the starting dose of Exelon is 1.5 mg BID; subsequently, the dose may be increased to 3 mg BID and further to 4.5 mg BID and 6 mg BID, based on tolerability, with a minimum of 4 weeks at each dose.

Exelon should be taken with meals in divided doses in the morning and evening.

Recommendations for Administration: Caregivers should be instructed in the correct procedure for administering Exelon Oral Solution. In addition, they should be directed to the Instruction Sheet (included with the product) describing how the solution is to be administered. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist (see PRECAUTIONS: Information for Patients and Caregivers).

Patients should be instructed to remove the oral dosing syringe provided in its protective case, and using the provided syringe, withdraw the prescribed amount of Exelon Oral Solution from the container. Each dose of Exelon Oral Solution may be swallowed directly from the syringe or first mixed with a small glass of water, cold fruit juice or soda. Patients should be instructed to stir and drink the mixture.

Exelon Oral Solution and Exelon Capsules may be interchanged at equal doses.

HOW SUPPLIED

Exelon® (rivastigmine tartrate) Capsules equivalent to 1.5 mg, 3 mg, 4.5 mg, or 6 mg of rivastigmine base are available as follows:

1.5 mg Capsule – yellow, "Exelon 1,5 mg" is printed in red on the body of the capsule.

Bottles of 60.....NDC 0078-0323-44
Bottles of 500.....NDC 0078-0323-08
Unit Dose (blister pack) Box of 100 (strips of 10).....NDC 0078-0323-06
Unit Dose Blister Card of 30.....NDC 0078-0323-15

3 mg Capsule – orange, "Exelon 3 mg" is printed in red on the body of the capsule.

Bottles of 60.....NDC 0078-0324-44
Bottles of 500.....NDC 0078-0324-08
Unit Dose (blister pack) Box of 100 (strips of 10).....NDC 0078-0324-06
Unit Dose Blister Card of 30.....NDC 0078-0324-15

4.5 mg Capsule – red, "Exelon 4,5 mg" is printed in white on the body of the capsule.

Bottles of 60.....NDC 0078-0325-44
Bottles of 500.....NDC 0078-0325-08
Unit Dose (blister pack) Box of 100 (strips of 10).....NDC 0078-0325-06
Unit Dose Blister Card of 30.....NDC 0078-0325-15

6 mg Capsule – orange and red, "Exelon 6 mg" is printed in red on the body of the capsule.

Bottles of 60.....NDC 0078-0326-44
Bottles of 500.....NDC 0078-0326-08
Unit Dose (blister pack) Box of 100 (strips of 10).....NDC 0078-0326-06
Unit Dose Blister Card of 30.....NDC 0078-0326-15

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in a tight container.

Exelon® (rivastigmine tartrate) Oral Solution is supplied as 120 mL of a clear, yellow solution (2 mg/mL base) in a 4-ounce USP Type III amber glass bottle with a child-resistant 28-mm cap, 0.5-mm foam liner, dip tube and self-aligning plug. The oral solution is packaged with a dispenser set which consists of an assembled oral dosing syringe that allows dispensing a maximum volume of 3 mL corresponding to a 6-mg dose, with a plastic tube container.

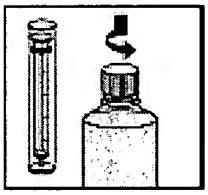
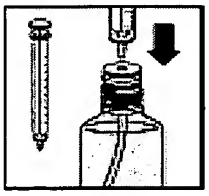
Bottles of 120 mL.....NDC 0078-0339-31

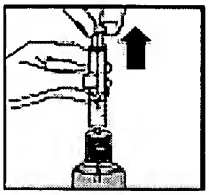
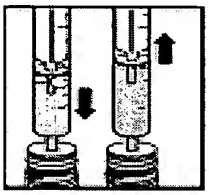
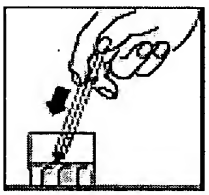
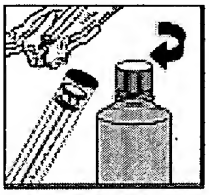
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in an upright position and protect from freezing.

When Exelon Oral Solution is combined with cold fruit juice or soda, the mixture is stable at room temperature for up to 4 hours.

REV: JUNE 2006 T2006-73

Exelon® (rivastigmine tartrate) Oral Solution
Instructions for Use

	1. Remove oral dosing syringe from its protective case. Push down and twist child-resistant closure to open bottle.
	2. Insert tip of syringe into opening of white stopper.

	3. While holding the syringe, pull the plunger up to the level (see markings on side of syringe) that equals the dose prescribed by your doctor.
	4. Before removing syringe containing prescribed dose from bottle, push out large bubbles by moving plunger up and down a few times. After the large bubbles are gone, pull the plunger again to the level that equals the dose prescribed by your doctor. Do not worry about a few tiny bubbles. This will not affect your dose in any way. Remove the syringe from the bottle.
	5. You may swallow Exelon Oral Solution directly from the syringe or mix with a small glass of water, cold fruit juice or soda. If mixing with water, juice or soda, be sure to stir completely and to drink the entire mixture. DO NOT MIX WITH OTHER LIQUIDS.
	6. After use, wipe outside of syringe with a clean tissue and put it back into its case. Close bottle using child-resistant closure.

Store Exelon Oral Solution at room temperature below 25°C (77°F) in an upright position. Do not place in freezer.

NOVARTIS

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CNS submissions

10 Years of EMEA CNS medicines – 3
Anti-dementia treatments

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Alzheimer's disease

Dementia is a chronic, progressive decline in cognitive function that afflicts 5% of the population over the age of 65 and progresses to more than 20% of those over 80. Alzheimer's disease (AD) is the commonest form of dementia accounting for 50% of all cases. Other common forms include vascular dementia caused by constriction or other interruptions of blood circulation in the brain and Lewy Body disease.

A definite diagnosis of Alzheimer's disease is only achieved at post-mortem examination where the characteristic pathological signs of neuritic plaques and neurofibrillary tangles are observed (Lobo et al, 2000).

Five variants of AD have been identified varying in age of onset, chromosomal linkage and pathology. Duke variant (60-80% of cases) is characterised by late and insidious onset and has the classic or typical pathology. Idiopathic AD accounts for up to 20% diagnoses (Fratiglioni et al, 2000). There is more to AD than impairment of short term and long term memory. In addition to the characteristic memory loss and impairment of thinking processes (cognitive function), there is often a notable increase in anxiety and fearfulness as well as agitation and even psychosis.

A rare form of the disease strikes before the age of 65 and has a more rapid and pervasive deterioration. This early-onset Alzheimer's (EOAD) is more common in individuals with a family history of the disease. This familial form has given researchers valuable clues in identifying likely genetic mutations that may contribute to susceptibility to AD. Data from a number of studies suggests that the disorder is more prevalent in women.

Educational level is inversely related to the risk of developing AD. Lower educational attainment and having an apolipoprotein E genotype are positively associated with increased risk of dementia (Kukull et al, 2002).

Two compounds have been the subject of successful Marketing Authorisation Applications to EMEA as treatments for dementia: Rivastigmine licensed in 1998 and Memantine licensed in 2002. The compounds have markedly different mechanisms of action (See Boxes 1 and 2) and are indicated for different stages of dementia. This article reviews the EPARs and the subsequent clinical and commercial success of these compounds.

Pre-clinical data

Mechanism of action

Rivastigmine

Rivastigmine binds to the catalytic binding site on the cholinesterase enzyme forming a carbamylated enzyme that slowly breaks down again into the free enzyme. The increase of ACh function is readily demonstrated in *in vitro* slice preparations. Chronic dosing of Rivastigmine to animals was shown to produce significant elevations in ACh levels in the brain, heart and in circulating blood. Rivastigmine reversed the impairments of memory function induced by administration of the muscarinic cholinergic antagonist scopolamine in rats tested in the Morris water maze test (Ballard and McAllister, 1999).

Memantine

Memantine was originally made by Eli Lilly (Parsons et al, 1999) and investigated as an anti-diabetic agent long before an application was made for its use as a treatment for organic brain syndrome by Merz in Germany in 1986 under the name of Akatinol Memantine®. Its mechanism of action was unknown at this stage but its beneficial effects on cognitive function prompted a clinic development exercise that resulted in this application to use Memantine as a treatment for dementia.

Pre-clinical studies have shown that it acted as an antagonist at the magnesium ion channel of the NMDA glutamate receptor. This was the same site of action as the dissociative anaesthetics, ketamine and phencyclidine (PCP). Clinical experience with Memantine, however, suggested that it did not possess the same hallucinogenic properties as these compounds. It seems to be a special feature of Memantine's activity that it is a relatively low affinity, highly voltage-dependent antagonist at NMDA receptors. It is perhaps this feature of Memantine that avoids the CNS side effects noted with ketamine and PCP (Parsons, et al, 1999).

Data in the dossier showed that Memantine prevented neuronal damage and memory deficits induced by bilateral carotid artery occlusion in rats. As the drug was administered prior to the ischemic insult the clinical relevance of this procedure is limited. What it did show, however, was that memantine could act as an NMDA antagonist *in vivo* and that it could act to prevent hyperglutamatergic neuronal activation and cell death. Memantine also showed a trend towards improved memory performance in the Morris water maze in aged rats and in animals that had received an experimental lesion to the entorhinal cortex. No evidence was reported on potential disruption of performance at higher doses. Memantine also showed some analgesic properties in rodent tests.

ADME toxicology

Rivastigmine

Oral bioavailability of Rivastigmine increased with dose in rats, dogs and humans, presumably due to a saturable first pass metabolism following absorption. The compound was extensively metabolised by cholinesterase-mediated hydrolysis in the liver. Urinary excretion accounted for >75% of elimination.

The acute and chronic toxicity of the compound was that expected of a cholinomimetic compound. Low LD_{50} values were obtained in rodents and dogs with tremor, convulsion and respiratory difficulties observed prior to mortality.

The clinical signs of excess pharmacology did diminish over time in the chronic dosing studies. However, the No Observed Adverse Event Level in rodents and the dog was 0.11mg/kg, which was less than the calculated maximum recommended human dose of 0.2mg/kg (based on a 60kg person).

Memantine

Studies in rats and humans showed good GI tract absorption of Memantine. Single and repeated administration studies in rats and baboons showed distribution throughout the body with some concentration in the lungs and kidneys. Infusion studies showed whole brain concentrations 44-fold higher than free serum levels. Plasma pharmacokinetics in the rat showed two peak concentrations at 30-60 mins and at 120-240 mins.

Hydroxylation appeared to be the main route of metabolism. None of the identified metabolites had any NMDA antagonist properties. Renal excretion accounted for 80-90% of memantine elimination in animals and in humans.

Toxicology in both acute and chronic studies was explicable in terms of the pharmacology of the compound. Ataxia, tremor and apnoea were noted on acute administration with convulsion observed at higher doses (>25mg/kg) in rodents and dogs. Chronic dosing also induced ataxia, apnoea and reduced food intake resulting in decreases in body weight. In a 12-month rat study lesions to ocular tissues were observed. Neuronal vacuolisation was observed in mice following administration of high doses of memantine in the diet.

Clinical pharmacology

Rivastigmine

A single dose of Rivastigmine was able to inhibit AChE in the periphery and CNS (as measured in cerebrospinal fluid) for up to 11.6 hours post administration. Rivastigmine showed non-linear kinetics with considerable variation in bioavailability. The half-life ($t_{1/2}$) was measured at 1 hour for a 3 mg dose (Table 1). Plasma levels were higher in elderly patients and subjects than in young volunteers.

Memantine

The applicant presented data from 25 PK/PD studies with a total of 434 subjects (377 Memantine-, vs 105 placebo-treated). No specific biomarker was identified as a surrogate for a therapeutic effect in healthy volunteers. Neither cognitive testing, EEG, neuroendocrine, nor sensory (pain) tests revealed any effect of doses up to 30mg IV.

Memantine achieved good bioavailability following oral dosing (100%) with a t_{max} following single oral doses of 10 and 40mg of 3 and 8 hours respectively. Steady state levels were achieved after approximately 11 days with accumulation in plasma reaching 3-4 times the C_{max} of a single dose. Plasma protein binding was similar to the pre-clinical values of 45%. A post-mortem on a female patient revealed brain regional concentrations from 0.1 to 0.5μg/g. The majority of Memantine was eliminated in urine (6-80%) with a terminal half-life of 60 to 100 hours (Table 1). Caution is therefore recommended when using the compound in renally impaired patients.

Clinical efficacy

Rivastigmine

Three Phase II studies in 566 patients suggested that 12mg/day was the maximum tolerated dose. Sixteen Phase III studies were conducted of which four randomised, placebo-controlled, multicentre trials with a duration of 26 weeks contributed to the efficacy data for Rivastigmine. Patients had mild to moderate dementia as rated on the MMSE (scores from 10-26). A number of rating scales were used each with different endpoints (see Table 2). Doses >6mg/day showed consistent efficacy across the endpoints vs placebo (see below for comments on rating scales). Lower doses 1-4mg/day did not yield significant improvements. Dropouts due to adverse events also increased with dose, again reaching significance vs placebo at doses >6mg/day.

Memantine

A large number of proof-of-concept trials were performed (21 in total) with small numbers of patients and little detail on the test systems used. Studies with n > 65 showed pro-cognitive effects for Memantine. Four main Phase III trials were presented, one in moderate to severe AD patients, one in a mixed AD and vascular dementia patient set, and two in patients with vascular dementia only (Table 3). MRZ-9605 was performed in accordance with advice provided by the CPMP in order to confirm the results of previous studies. It included measures of functional activity and global outcome as the primary endpoints. The studies showed some positive effects on specific endpoints for dementia of the Alzheimer's type but not for vascular dementia.

Clinical safety

Rivastigmine

Data from 3006 patients receiving Rivastigmine in all of the above therapeutic studies contributed to the safety database. 1249 patients received Rivastigmine for more than six months. There was no significant increase in mortality. 17% of patients on Rivastigmine across all studies dropped out due to adverse events compared to 8% on placebo. The primary adverse events (AEs) were nausea and vomiting, as would be expected from a cholinomimetic compound. These effects were often short in duration and averted by starting with lower doses and progressively increasing to the clinically recommended dose. Central and peripheral nervous system effects were also noted as were psychiatric disturbances including visual hallucinations. As hallucinations occur spontaneously with AD patients it is difficult to assess the role of Rivastigmine in their occurrence. Cardiac and respiratory effects did not figure highly in the reported AEs.

CNS submissions continued...

Memantine

The CPMP report states that over 100 million daily doses of Memantine have been sold in Germany. The clinical experience so far suggests that there is little cause for concern in using Memantine even in the frail, elderly target population. Seventy-three spontaneous adverse events have been reported for 48 patients. The most common events were restlessness (6), convulsions (4) and tremor (3). The adverse events can be avoided by commencing treatment on low doses (5mg) and titrating upwards to the clinically recommended dose (10-20mg). The German clinical experience will also be vital in helping clinicians in other countries to assess the place for Memantine in their pharmacopoeia.

Discussion

The effects with both compounds on cognitive function are modest, even small depending on the endpoint and measurement scale. Both compounds only delay the decline of cognition function and the effects vary enormously from patient to patient.

The fact that Rivastigmine requires some degree of ACh release, and a functioning postsynaptic system to have its effect means that it has been targeted at mild-to-moderate AD patients. In patients with advanced, severe AD there may be too little remaining cholinergic activity for Rivastigmine to augment. In contrast Memantine has only been approved for moderate to severe AD although its mechanism of action would suggest the possibility that it could delay disease progression more effectively if administered earlier. Thus, it is possible that the cholinesterase inhibitor class of compounds (including Donepezil and Galanthamine) may complement the clinical use of Memantine. However; it is not clear at what point patients might switch or even if there would be any additional benefit to combination therapy with both drugs. Combination trials for Memantine with a range of cholinesterase inhibitors are under way and initial results suggest that there may be some additional benefit to co-administering these compounds (Tariot et al, 2004).

The mechanism of action of Memantine suggests that it may have some neuroprotectant properties. This hypothesis was supported in the pre-clinical data where predosing animals with Memantine reduced neuronal cell death associated with experimentally-induced ischemia. The current licence for Memantine is for moderate to severe dementia when a significant percentage of the neuronal damage has already occurred. Any potential neuroprotectant effects of Memantine that may delay disease progression would potentially be more evident in the earlier stages of the disease. The FDA recently rejected a submission by Forest Laboratories for a licence to use Memantine (Namenda®) for the treatment of earlier stage mild to moderate dementia. This was based on the fact that significant efficacy was shown in only one of three studies submitted in support of the extended indication.

Alzheimer's disease is a pervasive disorder which profoundly alters mood and behaviour in patients. Although the primary focus of the clinical studies has been on memory loss it may be efficacy in these other areas that will determine whether the cost of treatment is justified by the benefit to the patient. Thus treatments that reduce paranoia, hallucinations or wandering but have only modest effects on memory function may be of considerable benefit to sufferers and their carers.

Rating scales: What do they tell us?

A very large number of rating scales are used across the trials with these two compounds. A small but statistically significant improvement on performance on a psychometric test such as the digit span test may be interesting but unlikely to help a patient live independently or to stay at home with an elderly partner as carer. Thus, it makes sense to use scales related to function in daily life rather than tests of cognitive function. Even with the more clinically focussed scales it can be difficult to determine the significance of a change in an overall score in a test like the Mini-Mental State Examination (MMSE). One could also ask if a 7-point scale such as the Clinical Global Impression (CGI) is a little too blunt an instrument to register subtle but perhaps useful drug effects.

Attempts are being made by regulatory bodies to introduce some harmony in the testing scales used in the evaluation of AD. The European Agency for the Evaluation of Medicinal Products suggested a responder for mild to moderate AD should meet three criteria: a 4-point improvement on ADAS-cog, improvement or stabilisation on a global clinical impression scale completed by a care giver (eg, CIBIC-plus) and improvement or stabilisation on a measure of daily activities (eg, PDS). For moderately severe to severe dementia only the latter two criteria would apply as further testing may not be feasible in this patient group.

The NICE advice on the use of treatments for AD among other issues, pointed out that although the scales used are indeed well validated there is considerable variability in the outcomes reported making mean scores difficult to interpret.

Questions on cost-effectiveness of treatments: the NICE approach

The Health Technology Assessment (HTA) report from NICE (2004) accepted that the published data suggested a positive clinical benefit for the available cholinesterase inhibitor compounds Rivastigmine, Donepezil and Galanthamine. The report's endorsement was qualified, however: Clinical efficacy had been assessed only over periods of six months to one year. As AD is a chronic condition which persists for years after diagnosis some index of the longer term efficacy and cost effectiveness of the compounds would be required. A subsequent assessment was commissioned which issued its interim report in March 2005. The same reported concluded on the basis of published data that Memantine also had some beneficial effects on global cognitive function but little effect on mood or behavioural outcomes.

The draft guidance issued in March 2005 found that none of the currently available treatments, cholinesterase inhibitors or Memantine, was cost effective over the longer term (O'Neill, 2005). The companies behind these molecules argue that significant benefits can be observed in subsets of patients. As no predictive test yet exists to determine which patients may benefit there may be an argument for starting patients on these treatments. Sponsoring companies have been given additional time to provide evidence

that means exist for detecting those patients more likely to respond to the particular drug treatments. Although some evidence for these markers exists, the accuracy and reliability of these tests, be they neuroimaging, psychometric or based on a biomarker strategy (eg, Adler et al, 2004), have yet to be validated in larger patient populations.

The problem posed by the NICE assessment may be that the hurdles for demonstrating efficacy of a drug for the treatment of AD have been raised significantly. If companies now have to demonstrate that their compounds have to show long term efficacy in AD the cost of such trials may render AD not an economically viable target for the development of new medicines (Lovestone, 2002).

Regulatory policy as much as technical or scientific factors may be key for both the use of existing treatments and in the development of new treatments for Alzheimer's disease in the next decade. It will be a fascinating debate between drug developers and regulatory authorities that we will watch with interest.

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CNS submissions continued...

Table 1 Clinical pharmacology data summary for Rivastigmine and Memantine

	T_{max}	$T_{1/2}$ (hrs)	% Protein Binding	Max Daily Dose
Rivastigmine	0.5-2.0	2	40	6mg bid
Memantine	3.0-7.0	60-80	45	10mg qid

Table 2. Summary of main efficacy trials for Rivastigmine application

Study	Description	Treatment (mg/day)	Duration (weeks)	No of Patients Randomised	
				Rivastigmine	Placebo
B351	Efficacy and safety Rivastigmine	Fixed dose 3, 6, 9mg/day vs placebo	26	529	173
B352	Efficacy and safety Rivastigmine	Individual MTD 1-4 and 6-12mg (bid)	26	434	235
B303	Efficacy and safety Rivastigmine	Individual MTD 1-4 and 6-12mg (bid)	26	486	239
B304 Interim Safety Report	Efficacy and safety Rivastigmine	Individual MTD 2-12mg (bid or tid)	26	229	117

Table 3. Summary of efficacy trials for Memantine application

Study	Description	Treatment (mg/day)	Duration (weeks)	No of Patients Randomised
MRZ-9605 (USA/1999)	Safety and Efficacy Moderately severe to severe AD	20mg	28	252
MRZ-9403 (Latvia/1994)	Safety and Efficacy Moderately severe to severe AD and Vascular Dementia	10mg	12	167
MRZ-9202 (UK/1994)	Safety and Efficacy Vascular Dementia	20mg	28	548
MRZ-9408 (France/1996)	Safety and Efficacy Vascular Dementia	20mg	28	288

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Box 1: Acetylcholinesterase Inhibitors

It was noted in the late 1970s that there were significant and selective deficits in the markers for activity of the neurotransmitter acetylcholine in the post mortem brains of patients who had died with dementia (See Coyle et al, 1983). This observation seemed to point to a scenario like that previously described for Parkinson's disease; where a specific group of cells in the base of the brain die off causing a deficit in the neurotransmitter dopamine. The strategy of treating the disease by replacing the missing transmitter by dosing patients with its metabolic precursor L-DOPA was a significant success. However, straightforward replacement of acetylcholine is not easy. Oral administration of acetylcholine would not achieve therapeutic brain levels due to the action of the blood-brain barrier. Dietary supplements with the synthetic precursor of acetylcholine, choline, may increase levels of the transmitter at the synapse but it is also very rapidly degraded by the enzymatic action of acetylcholinesterase (AChE). This suggested that a better means of elevating ACh levels would be to inhibit the action of this enzyme, hence the development of a class of AChE inhibitors. One such compound was known for some time, physostigmine, is too short acting to be of any therapeutic benefit but studies in animals had shown that it could improve performance, particularly in tests where memory had been impaired with cholinergic antagonists such as atropine.

A cholinesterase inhibitor tacrine (THA) sold under the name of Cognex in the USA, showed positive improvements in some patients. It was also associated with severe impairment of hepatic function and careful monitoring was required. Its utility did point to the viability of the cholinergic hypothesis as a means of treating Alzheimer's disease. In this context the development of an AChE inhibitor with a prolonged duration of action offered a high probability of ameliorating symptoms of AD. Aricept (Donepezil, E2020) a long acting acetylcholinesterase inhibitor was licensed in the UK as a once-a-day treatment for AD in 1997.

Box 2: NMDA receptor antagonism: Memantine and the Goldilocks Effect

Glutamate is the major excitatory transmitter in the brain. It is one of the transmitters required to activate the NMDA receptor complex by acting with its co-agonist glycine to open an ion channel allowing calcium to enter the cell. This ion flux is the basis of the electrochemical transmission of information by nerve cells. In states of hyperactivation, when there is an excess of glutamate in the synapse, too much calcium can enter the cell and interfere with normal information processing and at high concentrations it can cause excitotoxic damage. The corollary of this glutamatergic neurotoxicity hypothesis is that an antagonist at NMDA receptors may mitigate the damage caused by glutamate (Dingledine et al, 1999). Where there is too little glutamatergic activation of cells such as when the NMDA receptor is deficient or blocked by a drug other harmful consequences occur. For example when people take phencyclidine or ketamine, drugs that block the NMDA receptor, they can experience a range of symptoms from mild memory loss to profound hallucinations. Memantine seems to produce a "Goldilocks" effect of tuning the NMDA receptor to a "just right" level of activity between these two extremes.

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Key Words

Rivastigmine, Memantine, Rating scales, Alzheimer's disease.

Abstract

This article reviews the EPARs and the subsequent clinical and commercial success of Rivastigmine and Memantine, two compounds which have been the subject of successful Marketing Authorisation Applications to EMEA as treatments for dementia. A discussion on the meaning of rating scales used in the clinical assessment of this therapeutic area and on cost-effectiveness of treatments is also provided.

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